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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/564,407	07/03/2006	Akiko Itai	P29138	3483

7055 7590 12/11/2008

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EXAMINER	
DICKINSON, PAUL W	

ART UNIT	PAPER NUMBER
1618	

NOTIFICATION DATE	DELIVERY MODE
12/11/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/564,407	ITAI ET AL.	
	Examiner	Art Unit	
	PAUL DICKINSON	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 September 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17,21 and 24-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17,21 and 24-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/14/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's arguments, filed 9/8/2008, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objects are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Response to Arguments

Claim Rejections - 35 USC § 112, First Paragraph

The rejection of Claims 17, 21, and 24-30 under 35 U.S.C. 112, first paragraph, is maintained.

Applicant argues the specification explains how ultraviolet light induces secretion of TNF, IL-1, and bFGF, which result in the transformation and proliferation of melanocytes. This then results in the overproduction of dermal pigment, which moves to epidermal keratinocytes, thereby darkening the skin. Applicant argues that, In view of the cascade of events, compounds that inhibit the transformation and proliferation of melanocytes would be expected to prevent dermal pigmentation by the same pathway. Applicant further argues that the claims under consideration are not directed to an unlimited number of compounds, but are limited to compounds that are reasonably expected by the inventors to have actions similar to those of compound 50. Applicant argues that the Examiner has misunderstood Brown et al (Lancet Oncology, 2004), which teaches that photodynamic therapy for melanoma has not yet been pursued

substantially in any study because of the difficulty in achieving good penetration of light through pigmented lesions, and partly because of ethical considerations about the aggressive nature of the disease. This does not support the Examiner's conclusion that a non-surgical therapy that is effective against one form of skin cancer – actinic keratinosis – will not predictably be effective against another form – melanoma. Regarding the recitation of "prevention" in the instant claims, Applicant argues that requiring "prevention" to mean complete eradication is inconsistent with the art's use of the term "prevention." Applicant cites "Wikipedia: Sunscreen" and "Skin Cancer Prevention and Early Detection" taken from the American Cancer Society website for support.

Applicant's arguments have been fully considered but are not found persuasive for the following reasons:

Regarding the teaching of Brown et al, the reference teaches that photodynamic therapy of melanoma comprising administration of aminolevulnic acid has not been pursued partly because of the aggressive nature of the disease. This suggests that this treatment option, which is effective against other forms of skin cancer, is ineffective against melanoma in part because of melanoma's high rate of metastasis. The Examiner further cites Workman et al (Workman et al, Altered states: selectively drugging the Hsp90 cancer chaperone, TRENDS in Molecular Medicine, 2004, 10(2), 47-51), which teaches that most cancers are driven by multiple genetic abnormalities and, hence, a single drug is unlikely to be fully effective (see page 47, second paragraph). Formula (I) constitutes a broad genus of compounds (see ***New Grounds of***

Rejection: Claim Rejections - 35 USC § 112, Second Paragraph below). Applicant has not established a structure-function relationship between the compounds encompassed by Formula (I) and the treatment and/or prevention of dermal pigmentation and/or skin cancer.

Regarding the recitation of prevention, the Examiner appreciates the references cited by Applicant. The instant specification does not define "prevention" and this term has varying interpretations, as illustrated by the references cited by Applicant and Webster's Ninth new Collegiate Dictionary cited by the Examiner in the previous office action. The Examiner must therefore give this term its broadest reasonable interpretation. As stated in the previous office action, the broadest reasonable definition of prevention is "to keep from happening or existing", i.e. to completely eradicate.

Because of the unknown unpredictability of the art, and in the absence of experimental evidence, no one skilled in the art would accept the assertion that the instantly claimed agents could be predictably used for the treatment or prevention of dermal pigmentation and/or skin cancer with a compound of formula (I).

Claim Rejections - 35 USC § 102

The rejection of Claims 17, 21, 24-30 under 35 U.S.C. 102(b) as being anticipated by US 3332996 ('996) is maintained.

Applicant argues that '996 fails to disclose administration of Compound 50 in a "preventatively and/or therapeutically effective amount".

Applicant's arguments have been fully considered but are not found persuasive. As stated above, the specification is not enabling for the prevention of dermal pigmentation and/or skin cancer in a mammal and accordingly, is not enabling for a "preventatively" effective amount. '996 discloses a concentration of 10 micrograms per milliliter (see col 3, lines 57-70), which is consistent with Applicant's disclosure of therapeutically effective amounts of the compound.

New Grounds of Rejection

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 31-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for therapeutic treatment of melanoma by administration of Compound 50, does not reasonably provide enablement for therapeutic treatment of dermal pigmentation and/or skin cancer by administering a compound of formula (I), nor does the specification provide enablement for the preventive treatment of dermal pigmentation and skin cancer by administration of a compound of formula (I), including Compound 50. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to treat nor prevent dermal pigmentation and/or skin cancer by

administration of a compound of formula (I), commensurate in scope with these claims.

To be enabling, the specification of the patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).[1]

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by In re Wands, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing Ex parte Forman, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,
2) the amount of direction or guidance provided,
3) the presence or absence of working examples,
4) the nature of the invention,
5) the state of the prior art,
6) the relative skill of those in the art,
7) the predictability of the art, and
8) the breadth of the claims.

[1] As pointed out by the court in In re Angstadt, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not "experimentation".

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. In re Fisher, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the Wands factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill level

The invention relates to the treatment of dermal pigmentation and skin cancer. The relative skill of those in the art is high, that of an MD or PhD. That factor is outweighed, however, by the unpredictable nature of the art.

As illustrative of the state of the art, the examiner cites Brown et al (Brown et al, The present and future role of photodynamic therapy in cancer treatment, Lancet Oncology, 2004, 5, 497-508). Brown et al teaches that photodynamic therapy of skin cancer comprising administration of aminolevulinic acid (see page 500, treatment of skin cancer). This therapy, while being effective against actinic keratinosis, is not effective against melanoma (see ibid). A non-surgical therapy (for example, photodynamic therapy comprising administration of aminolevulinic acid) that is effective against one form of skin cancer will not predictably be effective against another form. The reference teaches that photodynamic therapy of melanoma comprising administration of aminolevulnic acid has not been pursued partly because of the aggressive nature of the disease. This

suggests that this treatment option, which is effective against other forms of skin cancer, is ineffective against melanoma in part because of melanoma's high rate of metastasis.

The Examiner further cites Workman et al (Workman et al, Altered states: selectively drugging the Hsp90 cancer chaperone, TRENDS in Molecular Medicine, 2004, 10(2), 47-51), which teaches that most cancers are driven by multiple genetic abnormalities and, hence, a single drug is unlikely to be fully effective (see page 47, second paragraph).

The Examiner further cites http://www.merck.com/mmpe/sec10/ch128/ch128e.html (accessed 3/25/2008). The reference teaches that about 50,000 new cases of melanoma occur yearly in the US, causing about 8000 deaths. The incidence is increasing at a faster rate than any other malignant tumor. Sun exposure is a risk, as is family history, increased numbers of melanocytic nevi, and the occurrence of lentigo maligna, large congenital melanocytic nevus, and the dysplastic nevus syndrome. For tumors of cutaneous origin (not CNS and subungual melanomas), survival rate varies depending on the thickness of the tumor at the time of diagnosis (see Table 1: Cancers of the Skin: 5-Year Survival for Malignant Melanoma, Relative to Thickness). Melanomas arising from mucous membranes have a poor prognosis, although they often seem quite limited when discovered. Once melanoma has metastasized, 5-yr survival is about 10%.

2. The breadth of the claims

The instant claims encompass treating and/or preventing dermal pigmentation and/or skin cancer with a compound of formula (I). Since the instant specification provides no limiting definition of the term "prevention", the examiner will adopt the broadest reasonable interpretation for same. Webster's Ninth New Collegiate Dictionary defines "prevention" as "to keep from happening or existing", i.e., to completely eradicate.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides no direction or guidance for the treatment and/or prevention of dermal pigmentation and/or skin cancer with a compound of formula (I)

Regarding treatment of dermal pigmentation and/or skin cancer, no reasonably specific guidance is provided concerning useful therapeutic protocols for treating dermal pigmentation and/or skin cancer with a representative number of compounds of formula (I), other than treatment of melanoma by administration of Compound 50. The latter is corroborated by the working examples. The instant disclosure provides no evidence to suggest that a representative number of compounds of formula (I) are capable of this unique activity, nor that the unique activity demonstrated for Compound 50 can be extrapolated to tumors having unrelated mechanisms of resistance, and thus does not meet the "how to use" prong of 35 USC 112, first paragraph with regard thereto.

Regarding prevention of dermal pigmentation and/or skin cancer, no

reasonably specific guidance is provided concerning useful therapeutic protocols for preventing dermal pigmentation and/or skin cancer. The claims are very broad insofar as they recite the "prevention" of dermal pigmentation and/or skin cancer, i.e., the complete eradication of same. While such "prevention" might theoretically be possible under strictly controlled laboratory conditions, as a practical matter it is nearly impossible to achieve in the "real world" in which patients live; recurrence is always a risk.

4. The quantity of experimentation necessary

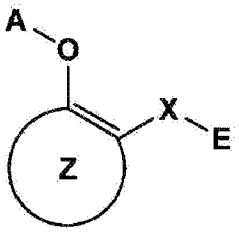
Because of the known unpredictability of the art, and in the absence of experimental evidence, no one skilled in the art would accept the assertion that the instantly claimed agents could be predictably used for the treatment nor prevention of dermal pigmentation and/or skin cancer with a compound of formula (I), as inferred by the claim and contemplated by the specification. Accordingly, the instant claims do not comply with the enablement requirement of §112, since to practice the invention claimed in the patent a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

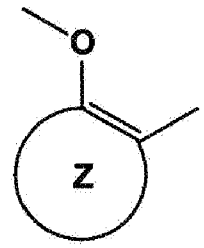
> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 17, 21, 24-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 17 recites "a compound represented by the following general formula (I) or a pharmacologically acceptable salt thereof,



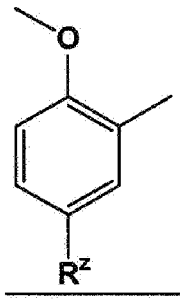
(I)

…the following partial formula (Iz-1) in the general formula (I) containing ring Z



(Iz-1)

represents the following formula (Iz-2):



(Iz-2)

wherein R^Z represents a halogen atom." It is unclear if formula (Iz-1) is a positive limitation of formula (I) for the following reasons: (1) It is unclear if partial formula (Iz-1) is the same formula as formula (I) only missing A, X, and E, or is some other fragment containing ring Z bearing a cis-1-methoxy-2-methyl vinyl moiety; and (2) the language "the following partial formula (Iz-1) in the general formula (I) containing ring Z… represents the following formula (Iz-2)…" suggests that the presence of formula (Iz-1) is optional, but when present, must be formula (Iz-2). Thus, what groups are and are not encompassed by Z in formula (I) is unclear.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 31-33 are rejected under 35 U.S.C. 102(b) as being anticipated by US 3332996 (hereafter '996). '996 discloses Compound 50 and its administration to skin (see col 2, lines 14-24; col 3, Table). The specification is not enabling for the prevention of dermal pigmentation and/or skin cancer in a mammal and accordingly, is not enabling for a "preventatively" effective amount. Regarding the therapeutically effective amount, '996 discloses a concentration of 10 micrograms per milliliter (see col 3, lines 57-70), which is consistent with Applicant's disclosure of therapeutically effective amounts of the compound.

Thus, '996 discloses the same active steps as the instant claims, and the results disclosed in the instant claims would be an inherent outcome of the administration. It is noted that In re Best (195 USPQ 430) and In re Fitzgerald (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter which there is reason to believe inherently includes functions that are newly cited or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that subject matter shown to be in the prior art does not possess characteristic relied on" (205 USPQ 594, second column, first full paragraph).

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will

the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to PAUL DICKINSON whose telephone number is (571)270-3499. The examiner can normally be reached on Mon-Thurs 9:00am-6:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

Paul Dickinson
Examiner
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December 5, 2008